Zacks Small-Cap Research

August 12, 2015
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Lipocine, Inc. (LPCN - NASDAQ)

LPCN: On Track Towards Filing NDA for LPCN 1021 with Enough Cash to Accelerate Programs for Lead Assets…

Current Recommendation	**Buy**
Prior Recommendation	N/A
Date of Last Change	09/24/2014
Current Price (08/12/15)	$17.37
Target Price	**$20.00**

UPDATE

On August 11, 2015, Lipocine, Inc. reported financial results for the second quarter 2015. The company reported no revenues as expected, and had a net loss of $4.2 million, or $0.26 per share.

We continue to remain advocates of Lipocine. For the purpose of this report, in addition to offering a financial and business review for the quarter, we would also like to offer an update regarding Lipocine's assets, and why we continue to remain optimistic regarding the Lipocine story. We still believe that the stock represents an attractive long-term investment opportunity, and are maintaining our price target of $20, and continue to rate the stock a 'Buy'.

SUMMARY DATA

52-Week High	**$17.37**
52-Week Low	**$3.95**
One-Year Return (%)	**101.74**
Beta	**3.29**
Average Daily Volume (sh)	**496,702**
Shares Outstanding (mil)	**18**
Market Capitalization ($mil)	**$316**
Short Interest Ratio (days)	**0.92**
Institutional Ownership (%)	**24**
Insider Ownership (%)	**15**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2015 Estimate	**N/A**
P/E using 2016 Estimate	**N/A**

Risk Level	**Above Average**
Type of Stock	**Small-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue
(In millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2014	$0.0 A	$0.0 A	$0.0 A	$0.0 A	$0.0 A
2015	$0.0 A	$0.0 A	$0.0 E	$0.0 E	$0.0 E
2016					$0.0 E

Earnings per Share
(EPS is operating earnings before non-recurring items)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2014	-$0.41 A	-$0.55 A	-$0.32 A	-$0.32 A	-$1.60 A
2015	-$0.23 A	-$0.26 A	-$0.37 E	-$0.40 E	-$1.30 E
2016					-$1.28 E

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WHAT'S NEW

Financial Review

On August 11, 2015, Lipocine (LPCN) reported financial results for the second quarter ending June 30, 2015. As expected, the company did not report any revenues in the quarter. Net loss was $4.2 million, or $0.26 per share, for the second quarter of 2015, as compared with a net loss of $7.0 million, or $0.55 per share, for the second quarter of 2014.

Research and development expenses were $3.2 million for the second quarter of 2015, compared with $6.0 million for the second quarter of 2014. This decrease in research and development expenses was due to reduced external service provider costs associated with clinical research and contract manufacturing costs. For the second quarter of 2015, general and administrative expenses were $1.1 million, compared to $1.0 million for the same period in 2014. R&D as well as G&A expenses were in-line with our expectations for the quarter.

As a reminder, Lipocine completed an underwritten public offering of 5.3 million shares of its common stock at $6.50 per share on April 29, 2015. Lipocine walked away with net proceeds of approximately $32.5 million after fees.

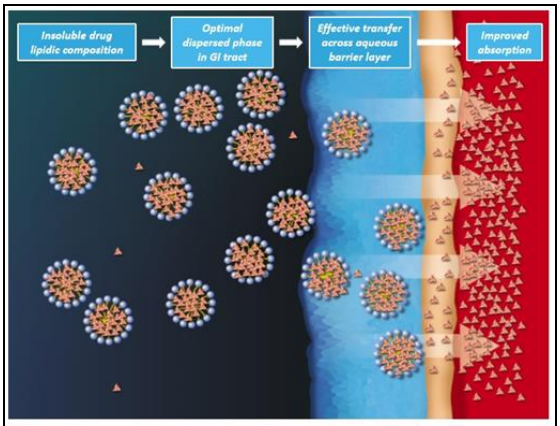
Operating burn for the second quarter of 2015 was $4 million. As of June 30, 2015, Lipocine had cash, cash equivalents, and marketable investment securities of $53.4 million, compared with cash and cash equivalents of $27.7 million as of December 31, 2014. This includes net proceeds of $32.5 million from the public offering mentioned above.

We continue to believe the current cash balance is sufficient to fund operations for the next two years. We believe that the recent completion of the public offering will allow Lipocine to step up development efforts of LPCN 1111 and LPCN 1107, in addition to focusing on the on-going pre-commercial LPCN 1021 activities. Assuming that LPCN 1021 is approved in 2016, we believe operating expenses will rise in anticipation of the company hiring an adequate sized sales force to promote the drug, in addition to expenses related to maintaining, expanding, and protecting its IP portfolio, and other activities to prepare for the commercialization launch.

As a reminder to investors, our update from March 2015 outlined the case for why we believe LPCN 1021, the company's oral testosterone replacement therapy, has significant potential for commercial success. Our update from July 2015 offered an update regarding Lipocine's assets, and why we continue to remain optimistic regarding the Lipocine story. We continue to believe the stock represents an attractive long-term investment opportunity, and will proceed to focus on second quarter 2015 highlights below.

A Brief Overview of Lipocine Inc.

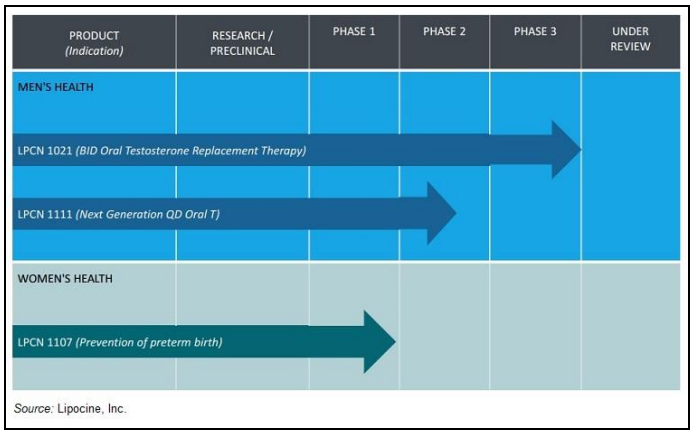
As way of background, Lipocine, Inc. is a specialty pharma company that has an oral drug delivery technology system, Lip'ral™, for products that affect the health of both men and women. The Lip'ral™ promicellar technology is a patented platform based on lipid compositions which form an optimal dispersed phase in the gastrointestinal environment for improved absorption of insoluble drugs (*below*).



Dispersion & Absorption in the Gastrointestinal Tract via Lip'ral

Source: Lipocine, Inc.

The company is currently developing three product candidates in conjunction with this system (LPCN 1021, LPCN 1111, and LPCN 1107) that are designed to enhance the pharmacokinetic parameters of the drugs, facilitate lower dosing requirements, reduce side effects, and limit gastrointestinal interactions that would otherwise decrease the effectiveness of the compounds (*below*).



An Update on LPCN 1021

Lipocine's lead asset, LPCN 1021, is a testosterone replacement therapy (TRT) designed for oral twice daily dosing in hypogonadal men with low testosterone. The company recently wrapped-up the extension study of a pivotal Phase 3 clinical trial run under protocols in-line with FDA guidelines for approval of TRTs. On April 30, 2015, Lipocine announced completion of the last patient visit in the safety assessment portion of its SOAR (Study of Oral Androgen Replacement) Phase 3 clinical study (NCT02081300). As a reminder, Lipocine announced positive top-line efficacy results from the study back in September 2014. SOAR evaluated the safety and efficacy of oral LPCN 1021 in hypogonadal men with low testosterone, and showed positive results with respect to the trial's primary efficacy endpoint with no serious drug related or cardiovascular adverse events to date.

In December 2014, Lipocine announced that the FDA confirmed that its ongoing SOAR design was acceptable for filing the new drug application (NDA) for the class TRT label. At that time, the FDA did not require any additional clinical studies for the NDA filing but did mention that supplementary data may be necessary if any safety concerns are uncovered during the SOAR Phase 3 analysis of results.

On March 24, 2015, Lipocine announced results from the March 19th pre-NDA meeting with the FDA. The purpose of the meeting was to discuss and evaluate the proposed LPCN 1021 NDA package, and to receive guidance on the 505(b)(2) filing and path to approval. As per the FDA's preliminary response, management did not expect to conduct any additional clinical studies other than the "food effect" study, which has always been a requirement for the expected submission of the NDA. The "food effect" study has now been completed, and we proceed to review the data from this study below. The outcome of the pre-NDA meeting was in-line with our expectations, and was welcome news for Lipocine since there was no requirement for a heart attack and stroke risk study or any additional safety studies prior to filing the NDA for LPCN 1021.

LPCN 1021 "Food Effect" Study

On June 15, 2015, Lipocine announced successful completion of its ongoing "food effect" study for LPCN 1021, which was conducted per the FDA requirement for submitting the NDA. The study was an open-label, randomized, four-period, four-treatment, crossover, single-dose trial evaluating bioavailability and pharmacokinetics of LPCN 1021 as a function of food fat content in hypogonadal males. The study was conducted at a single site and enrolled 14 hypogonadal males between the ages of 18 and 80, with 13 patients completing the study.

Patients received a single LPCN 1021 dose of 225 mg testosterone undecanoate, which was also the starting dose in the completed Phase 3 clinical study, under fasted conditions, and under the following three fed states approximately 30 minutes following an 800 to 1000 calorie meal:

- *Low Fat Meal*: 15% of calories from fat
- *Standard Fat Meal*: 30% calories from fat
- *High Fat Meal*: 50% calories from fat

Table 1: Comparative Pharmacokinetic Analysis for Testosterone Exposure following Administration of LPCN 1021 under Fed Conditions with Meals of Varying Fat Content (Study LPCN 1021-14-001, N = 13)

Parameter	Low Fat (~16.5 g) Meal[2]	Standard Fat (~30.1 g) Meal[1] (Reference)	High Fat (~53.5 g) Meal[3]
Cmax (ng/dL)			
Mean (% CV)	1570 (35%)	1560 (31%)	1680 (44%)
[Range]	[844 - 2610]	[746 - 2700]	[692 - 2910]
Point Estimate (90% CI bounds)	98.26 (82.18-117.48)	100	102.72 (85.92-122.82)
AUC 0-24h (ng*h/dL)			
Mean (%CV)	10429 (19%)	10421 (16%)	11974 (18%)
[Range]	[7529 - 14083]	[7817 - 14394]	[8729 - 15184]
Point Estimate (90% CI bounds)	98.86 (90.99-107.42)	100	114.06 (104.98-123.93)

Abbreviations: AUC =area under the curve; CI = confidence interval; Cmax = maximum observed serum concentration; CV = coefficient of variation

[1]30% total calories derived from fat content in the meal consistent with Phase 3 recommended meal

[2]15% total calories derived from fat content in the meal

[3]50% total calories derived from fat content in the meal

Source: Lipocine, Inc.

Results from the study showed that changes in meal fat content did not affect the bioavailability of testosterone from LPCN 1021, and also demonstrated comparable testosterone levels between the standard fat meal (similar to the meal instruction provided in the Phase 3 clinical study) and both the low and high fat meals. Similarly, testosterone levels were also comparable between the low fat and high fat meals. Based on Lipocine's comparative analysis of testosterone exposure from the study, LPCN 1021 bioavailability was not sensitive to low, standard, or high fat meal content. The table above outlines preliminary data for the pharmacokinetic parameters of maximum observed serum concentration (C_{max}) and area under the curve (AUC) for testosterone following administration of LPCN 1021 under fed conditions with meals of varying fat content. The table below shows that administration of LPCN 1021 under fasted conditions resulted in a significant reduction in bioavailability.

Table 2: Pharmacokinetic Parameters for Serum Total Testosterone following LPCN 1021 Administration under Fasted vs Fed Conditions in Hypogonadal Men

Parameter	Fasted (N = 14)	Fed[1] (N = 13)
Cmax (ng/dL)		
Mean (% CV)	562 (26%)	1680 (44%)
[Range]	[342 - 880]	[692 - 2910]
AUC 0-24h (ng*h/dL)		
Mean (% CV)	7423 (19%)	11974 (18%)
[Range]	[5597 - 10787]	[8729 - 15184]

Abbreviations: AUC =area under the curve; Cmax = maximum observed serum concentration; CV = coefficient of variation

[1] 50% total calories derived from fat content in the meal

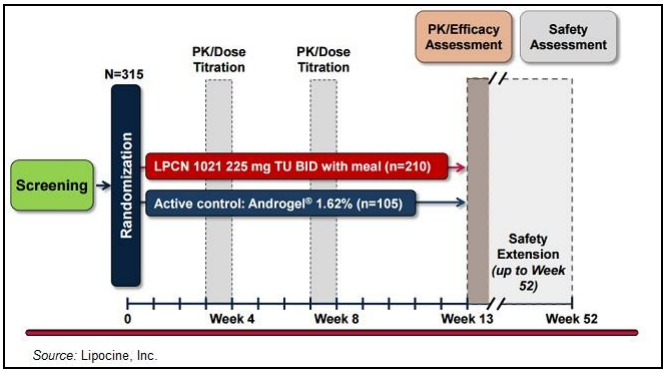
Source: Lipocine, Inc.

We view these preliminary results from the "food effect" study as excellent news for Lipocine as the study showed consistent and predictable therapeutic levels of testosterone when administered with a meal with no apparent significant sensitivity to meal fat content. As per previous guidance, we still believe that management plans to submit these preliminary results from the "food effect" study to the FDA for review and comment prior to submitting the NDA.

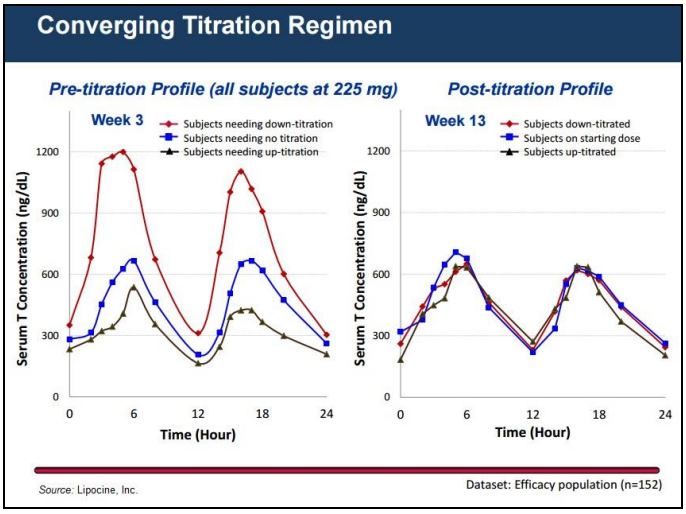
LPCN 1021 Safety Data from Phase 3 Trial

On June 29, 2015, Lipocine announced 52-week safety results from the SOAR Phase 3 clinical study evaluating efficacy and safety of LPCN 1021. LPCN 1021 was well-tolerated with no hepatic, cardiac or drug-related serious adverse events observed. We are happy to report that Lipocine released these results from the safety assessment portion of the SOAR trial according to the previously mentioned timeline.

SOAR was a randomized, parallel-group, active-controlled, open-label Phase 3 clinical study of oral testosterone replacement therapy (TRT) in hypogonadal males with low testosterone as indicated by a level of < 300 ng/dL. In total, 315 subjects at 40 different sites were randomized for a total of 52 weeks of treatment with 210 subjects randomized to receive LPCN 1021, while the remaining 105 subjects were randomized to receive the active control, Androgel®.



Although efficacy and safety were evaluated during the initial 13 weeks of the study, subjects continued to receive treatment through 52 weeks during a safety extension phase. All subjects that were randomized to receive LPCN 1021 were initially started at 225 mg testosterone undecanoate (TU) twice daily, which is equivalent to approximately 142 mg of testosterone twice daily. If needed, the dose was titrated up to 300 mg TU twice daily or down to 150 mg TU twice daily, and was dependent on serum testosterone levels measured during week 3 and week 7 (*below*).



All doses of LPCN 1021 or the active control were to be taken with a standard meal. We believe that the safety extension phase of the study was crucial in order to obtain important safety information regarding LPCN 1021 as well as the active control while subjects were on a stable dosing regimen. As per Lipocine, the subjects had a mean age of approximately 53 years, average body mass index (BMI) of 31 kg/m^2, and baseline testosterone of approximately 205 ng/dL with demographics and baseline characteristics being comparable between treatment groups. The company also reported that study discontinuation rates were similar across both groups.

…Adverse Events…

The safety population consisted of 314 subjects who received at least one dose of LPCN 1021. Of these patients, 210 subjects received LPCN 1021 and 104 subjects received the active control. The only adverse events that occurred in greater than 5% of subjects with either LPCN 1021 or the active control were:

- Upper respiratory tract infection: 5.2% with LPCN 1021 vs. 5.8% with active control
- Fatigue: 2.4% with LPCN 1021 vs. 6.7% with active control

It's also important to point out that serious adverse event and cardiac adverse event profiles were consistent between treatment groups, with none of the observed cardiac adverse events occurring in more than 1.0% of the subjects in the LPCN 1021 arm, and none were classified as severe. We believe that this is good news for Lipocine as no reported hepatic, cardiac, or drug-related serious adverse events were reported, and there were fewer cases of upper respiratory tract infections and fatigue reported in patients being treated with LPCN 1021 than the active control, Androgel®.

…Adverse Drug Reactions…

All observed adverse drug reactions were classified as being mild or moderate in severity and as per the company, no serious adverse drug reactions occurred during the 52-week treatment period. Adverse drug reactions such as peripheral edema, polycythemia, and thrombocytopenia occurred in 1% or fewer subjects with LPCN 1021, while those occurring in more than 2% of subjects with either LPCN 1021 or the active control were:

- Headache: 0.5% with LPCN 1021 vs. 3.9% with active control
- Acne: 2.9% with LPCN 1021 vs. 2.9% with active control
- Patient reported weight increase: 2.4% with LPCN 1021 vs. 0% with active control

Although patient reported weight increase was higher with LPCN 1021 as compared to the active control, the company reported that the overall mean weight change as compared to baseline was not significantly different between the treatment groups, and that weight changes greater than 10% from baseline over 52 weeks occurred in 2.3% of subjects with LPCN 1021 and 3.8% of subjects with the active control. Overall, we see the adverse drug reactions as being comparable to Androgel® based on these reported findings.

…Other Safety Parameters…

Lipocine also reported on several other safety parameters including blood pressure, lipid parameters, cardio biomarkers, and liver enzymes. As per the company, there were no significant changes in mean systolic and diastolic blood pressure from baseline in either treatment group. Mean values for the lipid parameters were not significantly different from baseline, except for high density lipoprotein (HDL) levels. Lipocine noted that mean HDL levels following LPCN 1021 treatment decreased slightly from baseline but were not significantly different from the active control after 52 weeks of exposure. Additionally, mean values for cardio biomarkers, hematocrit, hemoglobin, platelet count, prothrombin time, and prostate specific antigen were not significantly different from baseline, and mean values for liver enzymes remained within the normal range. Finally, mean dihydrotestosterone levels increased from baseline following LPCN 1021 treatment, but were comparable to changes seen with the active control.

Overall, we believe these results show that LPCN 1021 was well-tolerated during the 52 weeks of dosing with no hepatic, cardiac, or drug-related serious adverse events. All in all, we believe LPCN 1021 fared pretty well against the competition, and that the adverse event profile for LPCN 1021 is comparable to the active control, Androgel® 1.62%. We continue to believe the oral formulation of LPCN 1021, if approved, may improve patient compliance as it appears to be a generally safe, effective, and more convenient TRT option as compared to topical and injectable TRT products that are currently on the market.

It is important to mention that LPCN 1021 will have to adhere to all of the new regulations set forth by the FDA if approved. For instance, cautionary language will be required on the label for possible cardiovascular and stroke related risk with TRT, and the lack of benefit and safety of TRT in age-related hypogonadism. Additionally, Lipocine will have to conduct a well-designed trial to address the potential increased risk of heart attack and/or stroke in users of the product, but that will occur down the road. Lipocine has continually executed on the timeline previously laid out for developing LPCN 1021, and we still expect the NDA for LPCN 1021 to be filed with the FDA in the second half of 2015.

Update on LPCN 1107

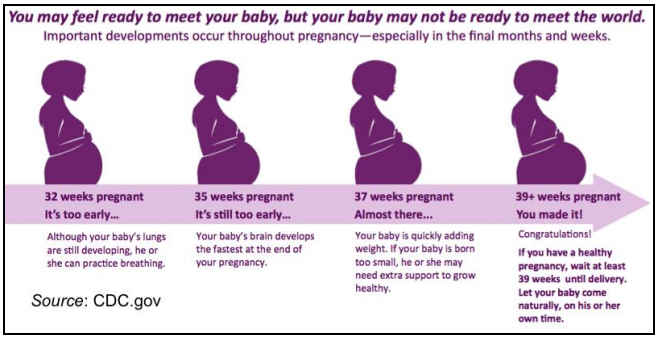
On June 2, 2015, Lipocine announced that the U.S. Food and Drug Administration (FDA) granted orphan drug designation to LPCN 1107, the company's oral hydroxyprogesterone caproate product candidate, a potential treatment for the prevention of preterm birth ("PTB"). We will proceed to provide a background on preterm birth and highlight how newly designated orphan drug LPCN 1107, in our opinion, further improves the fundamental outlook for the company. In order to obtain orphan drug exclusivity upon approval, we would like to mention that LPCN 1107 will need to demonstrate clinical superiority to the same drug already approved for the same orphan indication. This can be achieved, for instance, by demonstrating clinical superiority through establishing that the product offers a "major contribution to patient care."

Background on Preterm Birth

In humans, an ordinary pregnancy lasts 37 to 42 weeks, with the average being 40 weeks. A majority of babies born in the U.S. arrive near their due date, plus or minus a week or two. However, in approximately 12% of pregnancies,

babies are born prior to 37 weeks gestation, which is the definition of preterm birth. This represents approximately 500,000 babies, or one in every eight babies born in the U.S. According to Shali Mazaki-Tovi *et al.*, 2007, a woman delivering prior to 37 weeks is roughly four-times more likely to deliver a subsequent child preterm.

Preterm birth is associated with a wide range of problems, including breathing issues, feeding difficulties, cerebral palsy, developmental delay, vision problems, and hearing impairment. In addition, preterm birth remains the leading cause of infant mortality, accounting for as many as 75% of perinatal deaths (Ananth *et al*., 2006). As the following image from the CDC shows, although a baby's lungs are developed by 32 weeks into the pregnancy, a number of other development steps continue up through 39 weeks.



Along with the adverse health implications, preterm birth also has a substantial economic burden. According to the Institute of Medicine, in 2005, the costs associated with preterm birth totaled $26.2 billion, which is made up of the following:

- ✓ Medical services of $16.9 billion, with over 85% of those medical care services delivered in early infancy.
- ✓ Maternal delivery costs of $1.9 billion.
- ✓ Early intervention services of $611 million.
- ✓ Special education services associated with the higher prevalence of the four major disabling conditions among preterm infants (cerebral palsy, mental retardation, vision impairment, and hearing loss) of $1.1 billion.
- ✓ Lost household and labor market productivity associated with preterm births of $5.7 billion.

While taking into account special education services and lost productivity cost for the four major disabling conditions associated with preterm birth, we view this $26.2 billion figure to be a staggering number. However, it does not include the cost of medical care beyond early childhood or caretaker costs. For example, the first-year medical costs for PTB infants are 10 times higher than for full term infants. As such, we view the opportunity for a safe and effective therapeutic for the prevention of PTB as a billion-dollar market opportunity.

While the exact causes of preterm birth are still unclear, there are a number of known risk factors, which include:

- → Having a previous preterm birth
- → Carrying more than one baby
- → Chronic health problems in the mother (diabetes, high blood pressure, and clotting disorders)
- → Cigarette smoking, alcohol abuse, or illicit drug use during pregnancy

Hydroxyprogesterone Caproate for the Prevention of Preterm Birth

Currently, hydroxyprogesterone caproate is the only FDA approved treatment for the prevention of preterm birth. Several other compounds are used off-label, though the evidence of their efficacy from randomized controlled trials is lacking. Hydroxyprogesterone caproate (HPC) is a synthetic steroid hormone that is an ester derivative of 17α-hydroxyprogesterone formed from caproic acid. The drug was previously marketed by Bristol Myers Squibb under the trade name Delalutin® after being approved by the FDA in 1956.

In February 2011, the U.S. FDA granted approval to KV Pharmaceutical for Makena®, an intramuscular (IM) injection of HPC, for the prevention of preterm birth in women with a history of preterm delivery and a singlet pregnancy. The approval was based on a multicenter, randomized, vehicle-controlled, double-blind Phase 3 clinical trial conducted in 2003 (Meis *et al*., 2003). A total of 463 women enrolled in the study to receive either HPC (n=310) or placebo (n=153) at a dose of 250 mg administered weekly by intramuscular injection beginning at 16-20 weeks of gestation and continuing until 36 weeks of gestation or delivery.

In the study, 36.3% of births occurred before 37 weeks gestation in the HPC group, compared to 54.9% in the placebo group (P<0.001). Delivery before 35 weeks of gestation was also less frequent in the HPC group (20.6% vs. 30.7%, P=0.02) with an approximately 40% reduction in the rate of delivery before 32 weeks of gestation in the HPC group (11.4% vs. 19.6%, P=0.02). The following graph shows the percentage of women remaining pregnant as a function of gestational age.



Source: FDA Summary Review for Makena®

Prior to approximately 25 weeks gestation, a numerically greater proportion of subjects randomized to the HPC group delivered prematurely; after 28 weeks a greater proportion of subjects randomized to the control group delivered prematurely. The increased proportion of preterm births in the HPC-treated subjects prior to 25 weeks gestation was due, in part, to five miscarriages. Whether treatment with HPC contributed to the early pregnancy losses is not known at this time; however, this finding was not observed in the HPC-treated group from a smaller supportive study.

Prior to its approval by the FDA, hydroxyprogesterone caproate had been available through off-label use and prepared at pharmacies that compounded the agent into an injectable form at a cost of approximately $15 per injection. With 15 to 20 injections required for a full treatment course that put the cost of the drug at approximately $250-300 for a full-term pregnancy. However, Makena® was approved as an orphan drug, and upon approval KV Pharmaceuticals began charging $1,500 per injection, or approximately $25,000 for a full-term pregnancy. This pricing was heavily criticized, and in April 2011 the company announced they were lowering the price to $690 per injection. Still, the cost of a full-term pregnancy ranges between $11,000 and $14,000.

An Oral Formulation of HPC

Lipocine is developing LPCN-1107 as the first oral HPC for the prevention of preterm birth by formulating HPC with the Lip'ral™ technology. An oral formulation of HPC would offer a number of advantages over the current injectable formulation of the drug, including elimination of pain and reaction at the injection site as well as eliminating weekly trips to the doctor's office for administration of the compound.

LPCN-1107 was evaluated in a Phase 1 study in ten healthy, non-pregnant female volunteers where the study subjects received either one single dose of 400 mg of LPCN-1107 or two doses of LPCN-1107 administered 12 hours apart, followed by a single dose of 250 mg intramuscular HPC, with a one week washout period between each treatment. Results from the trial showed that there was significant absorption upon oral dosing of LPCN-1107 with a good dose response demonstrated as both C_{max} and AUC increased significantly from the single dose to the twice daily dose. The following chart shows that LPCN-1107 steady state 400 mg twice daily exposure was approximately 55% of weekly 250 mg intramuscular HPC. The Phase 1a data of healthy, non-pregnant women has been presented at the Society for Maternal-Fetal Medicine 35th Annual Meeting.

Steady state pharmacokinetic parameters - Geometric mean [min - max]		
Products / Dosing Regimen	**$C_{ss,max}$ (ng/mL) [range]**	**$AUC_{SS-1\ week}$(ng.h/mL) [range]**
LPCN 1107 400mg BID	23.9 [9.6 – 70.0]	1348 [673 - 3381]
Intramuscular injection, 250mg	17.8 [14.0 – 27.0]	2468 [1840 - 3180]

Source: Lipocine, Inc.

Positive Top-line Results in Phase 1b Study of LPCN-1107 In Pregnant Women

On January 12, 2015, Lipocine announced positive top-line results in a Phase 1b proof of concept study of LPCN-1107 for the prevention of preterm birth in pregnant women. The study was designed to determine the safety, tolerability, bioavailability and pharmacokinetics of LPCN-1107 as compared to an intramuscular HPC. The study was an open-label, three period, three treatment serial dosing study. Eight healthy pregnant women at 16 to 18 weeks gestation received three treatments in sequence. In period 1, patients received two doses of 400 mg oral LPCN-1107, administered 12 hours apart. In period 2, subjects received two doses of 800 mg oral LPCN-1107, administered 12 hours apart. Finally, in period 3, patients received a single dose of 250 mg HPC via intramuscular injection (the marketed product Makena®). Periodic blood sampling was collected over 24 hours following oral administration of the drug and over 28 days after the HPC IM dose.

Results from this study showed the first demonstration of HPC absorption following oral administration in healthy pregnant women. C_{MAX} and AUC for the oral administrations with LPCN-1107 are shown below (*below left*). LPCN-1107 dosing once adjusted to fall between 400 and 800 mg twice a day is expected to be comparable to the marketed 250 mg weekly IM product (*below right*).

Single Dose Pharmacokinetic Parameters

Dosing Regimen (BID) (N=7*)	C_{max} (ng/ml) [range]	AUC $_{0-24}$ (ng.h/ml) [range]
400mg	21.3	156
	[11.5 - 36.2]	[81 - 234]
800 mg	63.2	577
	[37.8 - 144]	[323 - 1365]

* one subject data analysis pending

Source: Lipocine, Inc.

Simulated Steady State Pharmacokinetic Parameters

Products / Dosing Regimen (N=7*)	$C_{ss,max}$ (ng/ml) [range]	AUC $_{SS}$ (ng.h/ml)# [range]
LPCN 1107 / 400mg BID	21.6	1074
	[12.1 - 36.2]	[573-1601]
LPCN 1107 / 800mg BID	71.1	4058
	[43.8 - 144.1]	[2180-7701]
Intramuscular injection / 250mg weekly	13.0	1817
	[6.5 - 29.4]	[805 - 3904]

* one subject data analysis pending

The relative bioavailability of oral to intramuscular administration was similar between pregnant and non-pregnant women (from the Phase 1a study in healthy, non-pregnant women) and can be seen below. Management believes that increasing the dose to the 550-600 mg range BID (from 400 mg BID) will allow for the proper efficacy. In this Phase 1b study, LPCN-1107 was well-tolerated with no serious adverse events observed.

Study population (N)	AUC $_{SS}$ (ng.h/ml)#		Relative bioavailability [oral / IM]
	LPCN 1107/ 400 mg BID Oral	Intramuscular Injection / 250 mg weekly	
Pregnant women (7*)	1074	1817	59 %
Non-pregnant women (10)	1348	2468	55 %

LPCN 1107 Phase 1 Study Results: Bioavailability in Pregnant and Non-Pregnant Women *Source:* Lipocine, Inc.

* one subject data analysis pending
# AUCss calculated for post steady state 1 week duration

LPCN 1107 Competitive Landscape

It is important to examine where LPCN-1107 may fit into the competitive landscape in comparison to the other treatment option currently available for prevention of preterm birth (PTB).

- AMAG Pharmaceuticals, Inc. recently acquired Lumara Health in November 2014 for $675 million in upfront payments with the potential of up to $350 million in contingent payments as certain sales milestones are achieved. Lumara Health is the exclusive marketer of Makena® (hydroxyprogesterone caproate injection), the only FDA approved product indicated to decrease the rate of PTB in women who are pregnant with one baby and who have delivered one preterm baby spontaneously in the past. Makena® is a weekly intramuscular injection (via 21 gauge needle) administered every seven days beginning between 16 and 20 weeks of gestation to alternating gluteus muscles. It significantly lowered the rate of preterm birth compared to women not on Makena®. According to Lipocine, the 2014 net sales of Makena® were roughly $165 million, with 2015 net sales projected to be anywhere between $245 and $270 million. Makena® has orphan drug exclusivity until 2018.

LPCN 1107: A Future Game Changer in the PTB Space

Approximately 12% of all pregnancies in the U.S. end in preterm birth, with approximately 40% of those having a history of spontaneous preterm birth. This equates to approximately 180,000 pregnancies annually that would be eligible for treatment with HPC. As noted above, prior to the approval of Makena®, HPC was available through compounding pharmacies and cost approximately $250-300 for a full course of treatment. KV Pharmaceuticals originally priced Makena® at $1,500 per injection, but due to a backlash they lowered the price to $690 per injection. At this price level, the cost would be between $11,000 and $14,000 for the 16-20 week treatment course. We believe the backlash over Makena® pricing was due to the undifferentiated aspect of the drug compared to what could be acquired for 1/100th of the cost prior to the approval of Makena®, and was not a function of the effectiveness of the drug.

Lipocine believes LPCN-1107 surpasses Makena® in several areas. First of all, LPCN-1107 is an oral formulation with the same API as Makena®, but does not require invasive, weekly injections, and therefore there is no potential for injection site reactions, excessive pain or infections from the weekly injections. This could eliminate anywhere from 18 to 22 injections. Furthermore, this would virtually eliminate the need for weekly doctor/nurse visits with an oral formulation as compared to an IM dose as well as the risk for pulmonary embolism. The most common side effects reported (vs. the control group) were injection site reactions and included pain (35%), swelling (17%) and other side effects such as urticaria (12%). Of those on Makena®, 35% of patients suffer from injection site pain, 17% from swelling and other possible serious side effects. As such, we believe that LPCN-1107 has the potential to become the first oral HPC product for the prevention of preterm birth in women with a prior history of at least one preterm birth. We have modeled the drug costing $5,000 per treatment course and with a 25% market share see the drug attaining approximately $250 million in peak revenues. We note that Lipocine has the potential to price the drug significantly higher than we currently model, potentially double our forecast. LPCN-1107 was granted Orphan Drug designation by the U.S. FDA on June 2, 2015.

Developmental Plans for LPCN 1107

Lipocine announced its development plans for LPCN 1107 on June 8, 2015. Lipocine received a Type C written response from the FDA that outlined next steps in the development of the product as a potential treatment for the prevention of preterm birth (PTB). Based on this FDA feedback, Lipocine plans to complete formulation optimization of LPCN 1107, and then will conduct a multiple-dose pharmacokinetic dose selection study in pregnant women. With two Phase 1 proof-of-concept studies in both pregnant and non-pregnant women completed, we believe that this dose selection Phase 2 study will commence in the fourth quarter 2015 or first quarter 2016. Once this study is completed, Lipocine plans to schedule an End-of-Phase 2 meeting with the FDA regarding the Phase 3 development plan. If all goes well, we believe that LPCN 1107 will be Phase 3 ready by mid 2016. We continue to believe that the area of preterm birth, even in countries as developed as the United States, is an area of unmet need, and at this point, we see a path forward for LPCN 1107, and look forward to watching the LPCN 1107 story unfold.

A Review of LPCN 1111

Positive Top-line Results in Phase 2a Study of LPCN 1111

As a reminder, on October 13, 2014, Lipocine announced positive top-line results in a Phase 2a study of LPCN 1111, a next-generation oral TRT that has the potential for once daily dosing. This study was an open-label, dose-escalating single and multiple dose study. Subjects received a single dose of 330 mg, 550 mg, or 770 mg of LPCN 1111 followed by once daily dosing of 550 mg for 28 days in 10 subjects and once daily administration of 770 mg for 28 days in eight subjects.

Results showed that a single daily oral dose of LPCN 1111, a novel prodrug of testosterone for oral delivery through the proprietary Lip'ral technology, provided testosterone levels in the eugonadal range, with good dose response and no subjects exceeding peak serum testosterone concentrations of 1500 ng/dl. In addition, LPCN 1111 was well tolerated with no significant adverse events reported. The following table gives a summary of the C_{AVG} and C_{MAX} data.

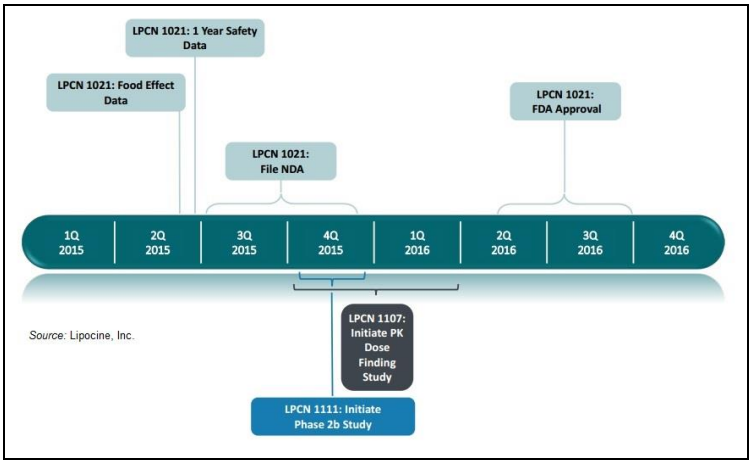
Measure	550mg QD	770mg QD	*Typical FDA targets for approval of TRT*
% subjects with C_{avg} within normal range	67%	88%	≥ 75%
% of subjects with C_{max} ≤1500ng/dL	100%	100%	≥ 85%
% of subjects with C_{max} between 1800ng/dL and 2500mg/dl	0%	0%	≤ 5%
% of subjects with C_{max} > 2500ng/dL	0%	0%	0%

Source: Lipocine, Inc.

As shown in the table, the 770 mg dose QD (once daily) resulted in 88% of subjects within the normal range, which is above the FDA target of 75% of subjects. The fact that testosterone levels could be achieved in the normal range with no subjects developing abnormally high testosterone levels is quite encouraging as a once daily dosing TRT would be clearly differentiated in the marketplace. Secondary safety data on C_{MAX} also looks outstanding. Based on these results, a Phase 2b trial is currently expected to begin in the fourth quarter of 2015 or the first quarter of 2016. We still believe that Lipocine needs some clarification from the FDA on the language of the TRT class label with the goal of determining optimal once daily dosing of LPCN 1111. This is expected to occur at some point in the third quarter of 2015. As per management guidance, LPCN 1111 is about 24 months behind LPCN 1021. In our view, based on Phase 2a data, this drug looks like a potential game-changer for TRT.

Conclusion & Recommendation

With all of the positive news for Lipocine over the past two quarters, we remain convinced that the company continues to move even close to the NDA submission for lead asset LPCN 1021. The market has begun to appreciate this as well, as the share price has increased nearly 160% since our March 2015 report! We remain big fans of Lipocine as an investment in the specialty pharmaceutical sector. We would like to bring attention to several near term value drivers, which are outlined below:



Full data from the recently completed Phase 3 clinical trial with LPCN 1021 was presented at the American Urological Association annual meeting in May 2015. The company is currently preparing the NDA to seek approval for LPCN 1021, and is still on track to submit the application to the U.S. FDA in the next few months. We expect LPCN 1021 will see U.S. approval around the middle of 2016, and model peak U.S. sales in the $400-500 million range. We remind investors that there is a second-generation version of the drug, LPCN 1111, currently in Phase 2 trials that could expand the potential peak U.S. sales to over $600 million. We believe that LPCN 1111 is roughly 24 months behind LPCN 1021 in development. Additionally, it is important to point out that LPCN 1111 is intended to be a once daily dosing product, as compared to the twice daily dosing profile of LPCN 1021.

We believe the news that LPCN 1107 has received U.S. orphan drug designation is a significant positive for the company. It not only protects the intellectual property of the drug, but also allows for aggressive pricing and reduced development and regulatory costs. As noted above, we model peak U.S. sales of LPCN 1107 of approximately $275 million. We look forward to the dose selection Phase 2 study to commence in the fourth quarter 2015 or first quarter 2016.

As a reminder, on April 29, 2015, Lipocine completed an underwritten public offering of 5.3 million shares of its common stock at $6.50 per share. Lipocine received net proceeds of approximately $32.5 million after fees. As a result of the public offering, and as of June 30, 2015, Lipocine had cash, cash equivalents, and marketable investment securities of $53.4 million. We believe the current cash balance is sufficient to fund operations for the next two years, assuming that LPCN 1021 is approved in 2016.

Although the current market capitalization is over $345 million, and has increased over 55% since our last update at the end of July 2015, we still view the shares as undervalued. We have updated our NPV analysis on the three product candidates discussed above, and our analysis pegs fair value at about $390 million, or approximately $20 per share, and we are maintaining a 'Buy' rating on the stock. We still believe that Lipocine represents a very attractive investment opportunity at the current price.

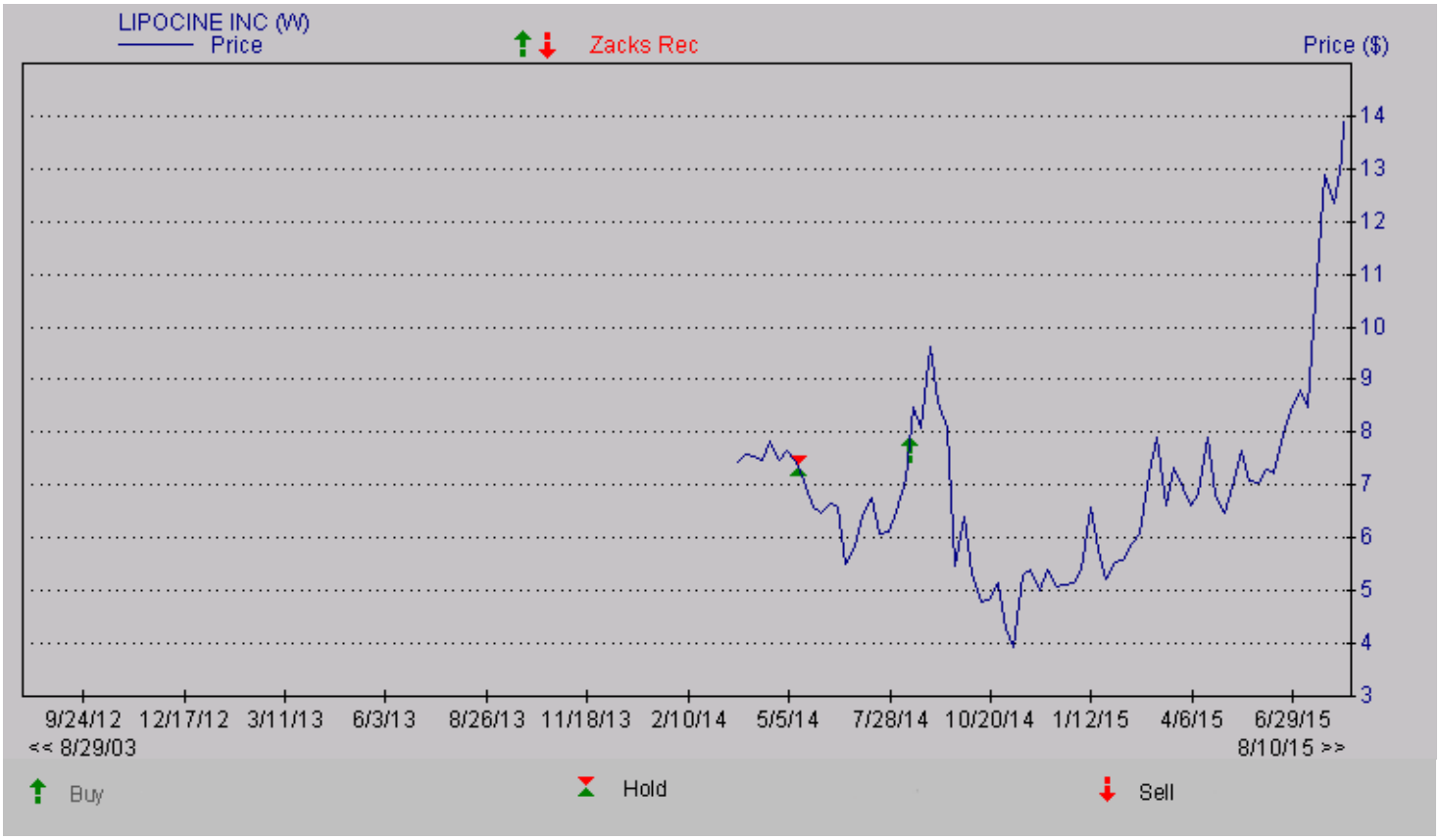
PROJECTED FINANCIALS

Lipocine, Inc.
Income Statement

Lipocine Incorporated	2014 A	Q1 A	Q2 A	Q3 E	Q4 E	2015 E	2016 E
LPCN 1021	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-
LPCN 1111	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth							
LPCN 1107	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth							
Total Revenues	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
CoGS	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	-					-	-
R&D	$15.5	$1.9	$3.2	$5.2	$6.0	$16.3	$18.0
SG&A	$5.0	$1.1	$1.1	$1.5	$1.6	$5.3	$7.5
Other expenses	$0.0	$0.0	$0.0	$0.0	$0.0	$0.1	$0.1
Operating Income	($20.5)	($3.0)	($4.3)	($6.7)	($7.6)	($21.7)	($25.6)
Operating Margin	-					-	-
Total Other Income	$0.1	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Pre-Tax Income	($20.4)	($3.0)	($4.2)	($6.7)	($7.6)	($21.6)	($25.6)
Taxes & Other	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	($20.4)	($3.0)	($4.2)	($6.7)	($7.6)	($21.6)	($25.6)
Reported EPS	**($1.60)**	**($0.23)**	**($0.26)**	**($0.37)**	**($0.40)**	**($1.30)**	**($1.28)**
YOY Growth	-						-
Shares Outstanding	12.8	12.8	16.5	18.2	18.8	16.6	20.0

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